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Prognostic Value of Heart Rate Adjustment of Exercise-Induced ST Segment Depression in the Multiple Risk Factor Intervention Trial

PETER M. OKIN, MD, FACC, GREG GRANDITS, MS,* PENTTI M. RAUTAHARJU, MD, PhD, FACC,† RONALD J. PRINEAS, MD, PhD, FACC,‡ JEROME D. COHEN, MD,§ RICHARD S. CROW, MD,|| PAUL KLIGFIELD, MD, FACC*

New York, New York; Minneapolis, Minnesota; Winston-Salem, South Carolina, Miami, Florida; and Saint Louis, Missouri

Objectives. **We sought to assess the effect of heart rate adjustment of ST segment depression on risk stratification for the prediction of death from coronary artery disease.**

Background. **Standard analysis of the ST segment response to exercise based on a fixed magnitude of horizontal or downsloping ST segment depression has demonstrated only limited diagnostic sensitivity for the detection of coronary artery disease and has variable test performance in predicting coronary artery disease mortality. Heart rate adjustment of the magnitude of ST segment depression has been proposed as an alternative approach to increase the diagnostic and prognostic accuracy of the exercise electrocardiogram (ECG).**

Methods. **Exercise ECGs were performed in 5,940 men from the Usual Care Group of the Multiple Risk Factor Intervention Trial at entry into the study. An abnormal ST segment response to exercise was defined according to standard criteria as $\geq$100 μV of additional horizontal or downsloping ST segment depression at peak exercise. The ST segment/heart rate index was calculated by dividing the change in ST segment depression from rest to peak exercise by the exercise-induced change in heart rate. An abnormal ST segment/heart rate index was defined as >1.60 μV/beats per min.**

Results. **After a mean follow-up of 7 years there were 109 coronary artery disease deaths. Using a Cox proportional hazards model, a positive exercise ECG by standard criteria was not predictive of coronary mortality (age-adjusted relative risk [RR] 1.5, 95% confidence interval [CI] 0.6 to 3.6, $p = 0.39$). In contrast, an abnormal ST segment/heart rate index significantly increased the risk of death from coronary artery disease (age-adjusted RR 4.1, 95% CI 2.7 to 6.0, $p < 0.0001$). Excess risk of death was confined to the highest quintile of ST segment/heart rate index values, and within this quintile, risk was directly related to the magnitude of test abnormality. After multivariate adjustment for age, diastolic blood pressure, serum cholesterol and cigarettes smoked per day, the ST segment/heart rate index remained a significant independent predictor of coronary death (RR 3.6, 95% CI 2.4 to 5.4, $p < 0.001$).**

Conclusions. **Simple heart rate adjustment of the magnitude of ST segment depression improves the prediction of death from coronary artery disease in relatively high risk, asymptomatic men. These findings strongly support the use of heart rate–adjusted indexes of ST segment depression to improve the predictive value of the exercise ECG.**

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The exercise electrocardiogram (ECG) remains the most widely used, noninvasive method for the evaluation of patients with known or suspected coronary artery disease. However, standard ST segment depression criteria based on achievement of a fixed magnitude of horizontal or downsloping ST segment depression have demonstrated only limited diagnostic sensitivity for the detection of coronary artery disease (1–4) or for risk stratification (5–13). Although heart rate adjustment of ST segment depression improved the sensitivity of the exercise ECG for the detection of coronary artery disease in selected patient groups (14–26) and improved the prediction of nonfatal coronary artery disease events in a low risk cohort of men and women from the Framingham Offspring Study (13), the prognostic value of heart rate–adjusted ST segment depression in clinically relevant patient groups at higher risk of coronary death has not been examined. Therefore, the purpose of this study was to compare performance of the simple ST segment/heart rate index with standard exercise ECG test criteria for the prediction of coronary artery disease death in high risk, asymptomatic men from the Usual Care Group of the Multiple Risk Factor Intervention Trial (MRFIT).

From the Division of Cardiology, Department of Medicine, The New York Hospital–Cornell Medical Center, New York, New York; *Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis, Minnesota; †EPICARE Center, Bowman Gray University, Winston-Salem, South Carolina; ‡Department of Epidemiology and Public Health, University of Miami School of Medicine, Miami, Florida; §Saint Louis University, Saint Louis, Missouri; and ||Laboratory of Physiological Hygiene, School of Public Health, University of Minnesota, Minneapolis, Minnesota. This study was supported by a grant from The Michael Wolk Heart Foundation, Inc., New York, New York.

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Address for correspondence: Dr. Peter M. Okin, The New York Hospital–Cornell Medical Center, 525 East 68th Street, New York, New York 10021.

Methods

Study group. The MRFIT was a randomized clinical trial in which 12,866 men between the ages of 35 and 57 years,

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without evidence of coronary artery disease by history, physical examination or abnormal Q wave on the rest ECG, were enrolled and randomly assigned to either a Special Intervention Group or Usual Care Group (27). The eligibility criteria, statistical design considerations and study methods have been previously described in detail (10,27–30). Selection criteria included use of a multiple logistic risk function, based on Framingham study data, to select subjects in the upper 15% (later changed to 10%) of risk of developing coronary artery disease on the basis of serum cholesterol concentration, diastolic blood pressure and cigarette smoking. Men with clinically evident coronary artery disease, diastolic blood pressure ≥115 mm Hg, serum cholesterol ≥350 mg/dl or serious life-limiting conditions were excluded from the trial. Both study groups were called back for annual examinations. Physicians caring for the Usual Care Group participants were informed of the baseline and annual examination results if a participant so requested, including a clinical interpretation of the ECG exercise test by the supervising study physician.

The present report deals exclusively with the 6,438 men in the Usual Care Group, because this group was not systematically exposed to a risk factor reduction program that might confound the prognostic value of the baseline exercise ECG (30). Of the 6,205 participants in this group who underwent exercise testing at baseline, 265 (4.3%) were excluded from the present analysis, including 55 with technically inadequate ECG tracings and 210 with inadequate ECG data to allow for heart rate-adjusted ST segment depression criteria to be calculated. Thus, included in the present study were 5,940 asymptomatic, high risk men in the Usual Care Group who underwent ECG treadmill exercise testing with subsequent 7-year follow-up.

Exercise electrocardiography. The Mason-Likar modification of the limb electrode positions (31) was used to record both rest and exercise ECGs. Rest ECGs were classified as abnormal by the Minnesota Code (32), as previously reported (10,29). Submaximal ECG exercise testing was performed on a treadmill with a stepwise increase in the slope and speed of the treadmill. Age-adjusted target heart rates, based on 85% of the predicted maximal response (10), were sought as the exercise end point, but exercise was terminated when necessary for clinical reasons, including the development of limiting fatigue, significant symptoms, observed ST segment depression ≥0.1 mV at 80 ms after the J point, systolic blood pressure >250 mm Hg, a decrease in systolic blood pressure with exercise or technical problems (10). Electrocardiograms, including leads aVL, aVF, V_4, V_5, V_6 and bipolar CS_5 and orthogonal leads X, Y and Z, were recorded in the sitting position immediately before exercise, at peak exercise and in the immediate recovery period in the sitting position.

Electrocardiographic data recorded on FM cassettes were analyzed by computer at the ECG Center in Halifax, as previously described (10). Data from the pre-exercise period, the last 30 s of exercise and the immediate recovery period were digitized at 500 Hz after prefiltering with a 125-Hz, low pass filter, with selective averaging of the complexes to reduce baseline noise. ST segment depression was measured by computer to the nearest μV at a point 75 ms after the J point. Exercise tests were evaluated by standard ECG criteria measured from the peak exercise tracings (1,24). The test was considered positive in the presence of an additional 100 μV (0.1 mV) of horizontal or downsloping ST segment depression at the end of exercise, correcting for any rest ST segment depression in that lead on the sitting pre-exercise ECG (13,24,26,33). For determination of both standard and heart rate-adjusted criteria, only additional ST segment depression below the isoelectric baseline was used; all rest ST segment elevations were normalized to the zero baseline, as previously described (33).

The ST segment/heart rate index was calculated by dividing the maximal, additional ST segment depression at the end of exercise, corrected for any rest ST segment depression in that lead on the sitting pre-exercise control ECG, by the exercise-induced change in heart rate (13,24). Based on previous studies (13,24), a positive ST segment/heart rate index was defined as ≥1.60 μV/beats per min. Calculation of the maximal ST segment/heart rate slope was not performed in this study because the intermediate-stage exercise heart rate and ST segment depression measurements necessary for calculation of the linear regression-based ST segment/heart rate slope (24) were not among the variables originally selected for computer analysis (10).

Definition and determination of coronary deaths. Six- to eight-year follow-up vital status was ascertained using previously reported methods (28). Cause of death was determined by a panel of three cardiologists who were otherwise unaffiliated with the MRFIT clinical centers and who were blinded to study group assignment. Coronary artery disease deaths were subclassified as documented myocardial infarction; sudden death within 60 min or between 1 and 24 h of symptom onset without myocardial infarction; congestive heart failure due to coronary artery disease; or death associated with coronary artery bypass surgery (2,10).

Statistical methods and data analysis. Cumulative coronary artery disease death rates for positive and negative exercise test variables are initially reported as raw event rates, with relative risk of a positive test and its 95% confidence interval (CI) (34). Event-free survival rates according to each method were plotted according to the Kaplan-Meier method (35), with comparisons of event-free survival between positive and negative tests performed with the log-rank test (36). The relation between a positive test by standard criteria and an abnormal ST segment/heart rate index and subsequent occurrence of coronary mortality was further analyzed by fitting a Cox proportional hazards model to the data (37). Age, diastolic blood pressure, serum cholesterol concentration and the number of cigarettes smoked daily at study entry were used as covariates in each model, in addition to the presence of a normal or abnormal standard exercise ECG or ST segment/heart rate index. With the proportional hazards model, the estimated relative risk of the incidence of coronary artery disease death for a positive test outcome, compared with a negative test outcome, was computed as the antilog of the

Table 1. Cumulative Coronary Artery Disease Deaths, Death Rates and Relative Risks According to Exercise Test Criteria

	Event Rate					
	Positive Test		Negative Test			
Criteria*	No.	%	No.	%	RR	95% CI
Standard ECG	5/186	2.7	104/5,754	1.8	1.5	0.6–3.6
ST/HR index	39/729	5.3	70/5,211	1.3	4.0	2.7–5.8

*See text for criteria definition. CI = confidence interval; ECG = electrocardiogram; RR = relative risk; ST/HR = ST segment/heart rate.

estimated coefficient corresponding to the dichotomous variable (38). The 95% CIs for the increased risk associated with a positive test outcome were then calculated from the estimated coefficient for a positive test and its standard error (39). Subgroup analyses were performed for strata defined by the change in heart rate during exercise and the presence or absence of rest ECG abnormalities. Coronary artery disease death rates and relative risk estimates were also computed by quintile of the ST segment/heart rate index to determine the pattern of risk across levels of the ST segment/heart rate index.

Results

Prediction of coronary death by standard and heart rate–adjusted ST segment integral criteria. After a mean follow-up of 7 years, there were 109 coronary artery disease deaths. Cumulative mortality rates and relative risks according to exercise test response are compared in Table 1. Of the 5,940 men in the Usual Care Group considered for analysis, 186 (3.1%) had a positive test according to standard criteria, and 729 (12.3%) had a positive test by ST segment/heart rate index criteria. The cumulative risk of coronary death was significantly higher in men with a positive ST segment/heart rate index (5.4%) than in men with a negative ST segment/heart rate index (1.3%, chi-square = 57.0, $p < 0.0001$), and the relative risk of coronary death in patients with a positive test was four times that of patients with a negative test. In contrast, the risk of coronary artery disease death was not significantly greater among patients with a positive standard test compared with patients with a negative ECG exercise test (2.7% vs. 1.8%, relative risk 1.5, $p = 0.55$).

Risk stratification according to exercise test criteria was further examined with Kaplan-Meier survival curves (Fig. 1). When adjusted for time to occurrence of coronary artery disease death, an abnormal ST segment/heart rate index remained predictive of outcome, with significantly lower survival rates among patients with positive tests. In contrast, there was no significant difference in survival rates between patients with positive and those with negative standard exercise tests.

When risk was adjusted for age (Table 2), a positive ST segment/heart rate index remained an independent predictor of coronary artery disease mortality, with a relative risk of 4.1. In contrast, a positive test according to standard ECG criteria was not associated with a significant increase in coronary mortality. Because previous analyses demonstrated that an abnormal ST segment integral response to exercise was associated with a number of risk factors also known to be potential predictors of coronary mortality (10), the independence of the association of both a positive standard test and an abnormal ST segment/heart rate index response to exercise with coronary deaths was further examined by multivariate Cox regression (Table 2). After multivariate adjustment for age, diastolic blood pressure, serum cholesterol and cigarettes smoked per day at baseline, the ST segment/heart rate index remained a significant predictor of coronary artery disease death, with a relative risk of 3.6. In contrast, an abnormal test by standard ECG criteria did not significantly predict cardiac death after adjusting for these baseline risk factors.

Analysis by quintile of the ST segment/heart rate index showed that the increased risk of future coronary death resided within the highest quintile of the ST segment/heart rate index values, and within this quintile was directly related to the magnitude of test abnormality (Table 3). An ST segment/heart rate index between 1.2 and 1.6 μV/beats per min was associated with a relative risk of 3.1 for coronary death; an ST segment/heart rate index between 1.6 and 3.3 μV/beats per min was associated with a relative risk of 4.1; and an ST segment/heart rate index greater than the 3.3 μV/beats per min partition used to define the presence of anatomically extensive disease at angiography (22) identified a subset of asymptomatic men with a 10% cumulative incidence of coronary death, a greater than ninefold risk relative to patients with ST segment/heart rate indexes of 0. In contrast, there was no significantly increased coronary artery disease mortality risk across the first

Figure 1. Kaplan-Meier plots of cumulative survival according to exercise test criteria. ST/HR = ST segment/heart rate.

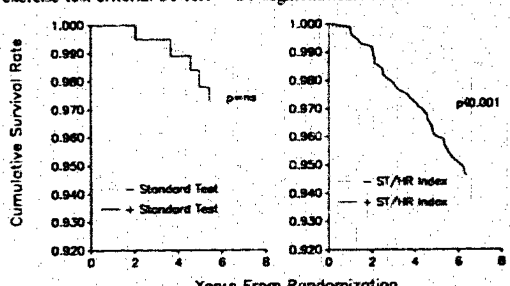

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Table 2. Age and Multivariate Cox Proportional Hazards Models for the Prediction of Coronary Artery Disease Death According to Exercise Test Criteria

Criteria	Chi-Square	p Value	RR	95% CI
Age-adjusted model				
Standard ECG	0.74	0.39	1.5	0.6–3.6
ST/HR index	49.1	<0.0001	4.1	2.7–6.0
Multivariate model*				
Standard ECG	0.61	0.43	1.4	0.6–3.5
ST/HR index	39.8	<0.0001	3.6	2.4–5.4

*Adjusted for age, diastolic blood pressure, serum cholesterol and baseline cigarette use. CI = confidence interval; ECG = electrocardiogram; RR = relative risk; ST/HR = ST segment/heart rate.

Table 3. Cumulative Coronary Artery Disease Death Rates and Relative Risks According to the Magnitude of ST Segment/Heart Rate Index

Quintile	ST/HR Index Values (μV/beats per min)	No.	%	RR	95% CI
1, 2	0	25/2,375	1.1	1.0	—
3	0.01–0.50	14/1,189	1.2	1.2	0.6–2.3
4	0.51–1.20	16/1,189	1.3	1.3	0.7–2.4
5a	1.21–1.60	15/458	3.3	3.1	1.6–5.8
5b	1.61–3.30	26/599	4.3	4.1	2.4–7.0
5c	>3.30	13/130	10.0	9.5	5.0–18.1

CI = confidence interval; RR = relative risk; ST/HR = ST segment/heart rate.

four quintiles of men with ST segment/heart rate index values between 0 and 1.2 μV/beats per min.

Relation of risk stratification to exercise change in heart rate and baseline electrocardiographic abnormalities. Because the magnitude of ST segment depression with exercise in patients with coronary artery disease is intrinsically related to the exercise-induced change in heart rate (40), the relation of risk stratification by standard criteria and the ST segment/heart rate index to the exercise change in heart rate was examined with men stratified according to the median heart rate change of 80 beats/min (Table 4). An abnormal ST segment/heart rate index significantly concentrated the risk of future cardiac death independent of exercise change in heart rate: the relative risk was 4.5 among patients with an exercise change in heart rate <80 beats/min and 3.2 in patients with greater changes in heart rate with exercise. In contrast, standard test criteria did not significantly concentrate risk in either heart rate increase subgroup.

The effects of the presence or absence of rest ECG abnormalities, as defined by the Minnesota Code, on the association of exercise ECG findings with coronary mortality are summarized in Table 5. Among men with normal exercise tests by either standard or ST segment/heart rate index criteria, the presence of rest ECG abnormalities did not affect the risk of coronary artery disease death. For men with positive exercise tests by standard criteria, there was a nonsignificant trend toward an increased risk of coronary death among patients with an abnormal, as compared with a normal, rest ECG. In contrast, the degree of risk concentration provided by an abnormal ST segment/heart rate index was similar in the presence or absence of rest ECG abnormalities: the 5.9% risk of coronary death in patients with both an abnormal ST segment/heart rate index and abnormal rest ECG was not significantly greater than the 5% risk associated with a positive ST segment/heart rate index in men with normal rest ECGs. There were similar findings for the ST segment/heart rate index when only the presence of ST segment depression on the rest ECG was considered. Among the 989 men with rest ST segment depression, the 4.2% (12 of 287) risk of coronary artery disease death in men with an abnormal ST segment/heart rate index was significantly higher than the 1.3% (9 of 702) risk in those with a normal ST segment/heart rate index (chi-square = 6.9, p = 0.009). Similarly, among the 4,951 men with no ST segment depression on their rest ECGs, the 6.1% (27 of 442) risk of death in patients with an abnormal ST segment/heart rate index was significantly greater than the 1.4% (61 of 4,509) risk in patients with a normal ST segment/heart rate index (chi-square = 49.5, p < 0.0001). It is important to note that there was no significant difference between the 4.2% risk associated with a positive ST segment/heart rate index in men with rest ST segment depression and the 6.1% risk in those with no ST segment depression on their rest ECGs.

Discussion

The findings of the present study extend the prognostic application of simple heart rate adjustment of exercise-induced ST segment depression from asymptomatic, low risk patients represented by the Framingham study patients (13) to relatively high risk, asymptomatic, middle-aged men. In addition to superior performance relative to standard ST segment depression criteria for the identification of patients with coronary artery disease (14–26), heart rate adjustment of ST segment depression by the ST segment/heart rate index provides additional prognostic information that outperforms widely used standard ST segment depression criteria, even after adjusting for established risk factors, and that is independent of the magnitude of change in exercise heart rate and of the presence or absence of rest ECG abnormalities.

Exercise electrocardiographic risk stratification. Test performance of standard ST segment depression criteria for the prediction of coronary events has been variable in previous studies (5–8,11–13). An ischemic ST segment response to exercise was a significant predictor of cardiac morbidity and mortality in the overall population of the Seattle Heart Watch (11), in a referred group of clinically normal male Air Force personnel (12) and in a prospectively matched study of asymptomatic normotensive patients (8). On the other hand, a positive test by standard test criteria did not significantly concentrate risk among the large subset of asymptomatic, healthy subjects in Seattle (11), did not concentrate risk in a nonreferred subset of normal pilots and astronauts undergoing

Table 4. Cumulative Coronary Artery Disease Death Rates and Relative Risks According to Exercise Change in Heart Rate Partitioned at the Median Change of 80 beats/min

	Event Rate							
	Positive Test		Negative Test					
Criteria	No.	%	No.	%	Chi-Square	p Value	RR	95% CI
Change in heart rate <80 beats/min								
Standard ECG	2/98	2.0	60/2,809	2.1	0.0	0.95	1.0	[illegible]
ST/HR index	26/401	6.5	36/2,506	1.4	42.2	0.0001	4.5	[illegible]
Change in heart rate ≥80 beats/min								
Standard ECG	3/88	3.4	44/2,945	1.5	1.0	0.32	2.3	0.7–7.2
ST/HR index	13/328	4.0	34/2,705	1.3	14.1	0.0002	3.2	1.7–5.7

CI = confidence interval; ECG = electrocardiogram; RR = relative risk; ST/HR = ST segment/heart rate.

exercise testing as part of a routine preflight assessment (12) and was not predictive of coronary events in over 3,000 asymptomatic men and women in the Framingham Offspring Study (13). In addition to the inherently low accuracy of standard test criteria, differences in study groups and differences in ST segment analysis and exercise methodologies may play a role in the varying prognostic power of traditional ST segment depression criteria in these studies.

In contrast, an ST segment/heart rate index partition of 1.60 μV/beats per min, previously found to identify the presence of coronary artery disease more accurately than standard ST segment depression criteria (24,26), significantly concentrated the risk of primarily nonfatal coronary events in asymptomatic men and women in the Framingham Offspring Study (13). Risk concentration by the ST segment/heart rate index in that study was independent of age and coronary risk factors and was independent of gender. However, the small number of coronary deaths in the Framingham cohort precluded meaningful subgroup analysis of the prediction of coronary artery disease death in this very low risk group of patients. The present report extends these observations by demonstrating that heart rate adjustment of the magnitude of ST segment depression using the ST segment/heart rate index stratifies the risk of coronary mortality and that the increased risk associated with an abnormal ST segment/heart rate index is independent of age, coronary risk factors, exercise change in heart rate and baseline ECG abnormalities. Further, ST segment/heart rate index values >3.3 μV/beats per min, previously demonstrated to be associated with anatomically extensive coronary artery disease (22), were associated with a nearly tenfold increased risk of coronary death over the follow-up period.

Previous evaluations of the ECG response to exercise in MRFIT examined the ST segment integral (10,30), which measures the time-voltage integral of the area between the isoelectric baseline and the ST segment (10,41), and demonstrated increased coronary mortality associated with this definition of abnormal exercise repolarization. However, this method has several limitations. First, the ST segment integral method has never achieved widespread use beyond application in MRFIT (10,30) and the Lipid Research Clinics Study (9). More importantly, analysis of the ST segment integral response to exercise appears to systematically underestimate the presence and severity of coronary artery disease in comparison to the simple magnitude of ST segment depression, particularly after heart rate adjustment (41). Moreover, heart rate

Table 5. Cumulative Coronary Heart Disease Death Rates and Relative Risk According to the Presence of Baseline Rest and Exercise Electrocardiographic Abnormalities

Electrocardiogram					
Rest	Exercise	No.	%	RR	95% CI
Standard ECG criteria (chi-square = 0.3, df = 3, p = NS)					
−	−	75/4,200	1.8	1.0	—
+	−	29/1,545	1.9	1.1	0.7–1.6
−	+	2/114	1.8	1.0	0.4–7.1
+	+	3/72	4.2	2.3	0.8–7.3
ST/HR index (chi-square = 57.9, df = 3, p < 0.0001)					
−	−	54/3,867	1.4	1.0	—
+	−	16/1,344	1.2	0.9	0.5–1.4
−	+	23/456	5.0	3.6	2.3–5.6
+	+	16/273	5.9	4.2	2.5–7.0

df = degrees of freedom; ECG = electrocardiographic; − = negative; + = positive.

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adjustment of the ST segment integral response to exercise has been shown to improve the prediction of coronary death compared with the simple ST segment integral alone in men in the Usual Care Group of MRFIT (42).

Heart rate adjustment of ST segment depression. Heart rate adjustment of the magnitude of ST segment depression represents a physiologic approach to interpretation of the ST segment response to exercise and improves assessment of the presence and severity of coronary artery disease (14–26,40). Application of heart rate–adjusted ST segment depression criteria is supported by a theoretical model based on solid angle theory and by experimental evidence linking the magnitude of ST segment depression recorded during exercise to both the anatomic extent of coronary artery disease and the degree of myocardial oxygen supply–demand imbalance (43–45), which is linearly related to change in heart rate (46). Thus, heart rate change during exercise, as an index of changing oxygen demand, adjusts evolving ST segment depression for the variable work load that accompanies exercise to provide a more accurate estimate of the presence and extent of coronary artery disease than traditional exercise test criteria based solely on the magnitude and configuration of ST segment depression (45). As a consequence, an abnormal ST segment/heart rate index is not dependent on achievement of 0.1 mV of ST segment depression during exercise. Although optimal accuracy of the exercise ECG in both men and women is obtained using the more complex, linear, regression-based ST segment/heart rate slope method (26), the simpler ST segment/heart rate index used in the present study is more generally applicable to retrospective analysis. Theoretical and experimental data relative to these methods have recently been reviewed in detail (40,45).

Clinical implications. The 5.3% seven-year risk of coronary artery disease death associated with an abnormal ST segment/heart rate index compares favorably with other potential risk stratifications in the current study group. Against a background of the 1.8% risk of death in the overall study group, none of the following significantly concentrated risk—an abnormal rest ECG (2% risk), an exercise change in heart rate <80 beats/min (2.1% risk), a positive test by standard criteria (2.7% risk), cigarette smoking (2.1% risk), a total cholesterol level ≥240 mg/dl (2%) or diastolic blood pressure ≥100 mm Hg (1.7% risk). Further, the decreased 7-year coronary artery disease mortality in the Special Intervention Group of men from MRFIT with an abnormal ST segment integral response to exercise, compared with the Usual Care Group (30), suggests that an aggressive risk factor reduction program may decrease the risk of coronary mortality in high risk men with exercise-induced ischemia. This highlights the importance of enhanced identification of patients at risk by the exercise ECG. The current data support the use of the simple ST segment/heart rate index for improved recognition of men at risk of coronary death and suggest the need for prospective evaluation of heart rate–adjusted methods, including the potentially more accurate ST segment/heart rate slope, for identification of those patients at high risk of coronary events.

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